PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Ralph R. WEICHSELBAUM *et al.*

Serial No. 08/289,290

Filed: August 11, 1994

For: CONSTITUTIVE GENE EXPRESSION IN CONJUNCTION WITH IONIZING RADIATION

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§ Group Art Unit: 1804
§
§ Examiner: B. Campell
§
§ Atty. Dkt.: ARCD:086/HYL

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Steven L. Highlander

BRIEF ON APPEAL

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BRIEF ON APPEAL

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the final Office Action mailed on July 7, 1997, regarding the above-captioned application. This brief is due on December 10, 1997, by virtue of the Notice of Appeal received on October 10, 1997. Included with this filing is the fee for the brief. Should appellants' check be missing or deemed deficient, or should other fees be deemed due, the Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Account No. 01-2508/ARCD:086/HYL.

I. STATUS OF THE CLAIMS

Claims 1-21 and 25-36 are pending in the application, claims 22-25 having been canceled. Appendix I contains a summary of the claims.

II. STATUS OF THE AMENDMENTS

An amendment is offered with the brief to address certain minor §112, second paragraph, issues (attached). Entry of the amendments is believed proper as they reduce the number of issues on appeal, introduce no new matter and raise no new issues.

III. REAL PARTY IN INTEREST

This application has been assigned to ARCH Development Corporation and licensed to GenVec.

IV. RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences for related cases.

V. SUMMARY OF THE INVENTION

The present invention is drawn to processes for inhibiting tumor growth and treating cancer in a human patient. In particular, the methods are drawn to provision to a cell of a gene encoding a radiosensitizing polypeptide, the gene being under the control of a constitutive promoter, and contacting said cell with ionizing radiation. The radiosensitizing polypeptide may be, in one example, tumor necrosis factor. Specification at page 5, lines 13-24.

In another embodiment, the present invention is drawn to methods of radioprotecting a cell from ionizing radiation. The process, more specifically, comprises transfecting the cell with a genetic construct comprising a gene encoding a radioprotective polypeptide linked to a constitutive promoter. Specification at page 5, lines 13-24.

In still another embodiment, methods are provided for increasing the level of a radioprotective or radiosensitizing polypeptide in a cell comprising administering to the cell a pharmaceutical composition comprising a gene encoding a radioprotective or radiosensitizing agent. Also encompassed is a method for assessing the response of a cell to the constitutive production of a radiosensitizing or radioprotecting factor comprising transfecting the cell with a genetic construct encoding a radioprotecting or radiosensitizing polypeptide. Specification at pages 65-66.

VI. ISSUES PRESENTED

A. Are claims 1-30 and 35 enabled?

B. Are claims 1-11 and 15-17 definite?

C. Are the claims obvious over the combined disclosures of Hallahan *et al.* I ("Hallahan I"), Hallahan *et al.* II ("Hallahan II"), Teng *et al.* ("Teng"), Neta *et al.* ("Neta"), Vile *et al.* ("Vile"), Felgner *et al.* ("Felgner"), Herz *et al.* ("Herz"), Breakfield *et al.* ("Breakfield") and Mattern *et al.* ("Mattern")?

VII. GROUPING OF THE CLAIMS

The claims do not stand or fall together as set forth in § IX, below.

VIII. SUMMARY OF THE ARGUMENT

The rejection under §112, second paragraph, and the rejection of claims 2-6 under §112, first paragraph, have been addressed by amendments that clarify the claims. The rejection of claims 1, 7-30 and 35, also under §112, first paragraph, is traversed on the grounds that the examiner has not made out a *prima facie* case of nonenablement based merely on the scope of the claims. First, appellants have provided a sufficiently enabling disclosure for the use of constitutively expressed TNF-α, in combination with radiation. This showing, in effect, provides proof of the principle that underlies the present invention. It would be a routine matter to screen other polypeptides that will, also in conjuction with radiation, effect (a) cell killing and (b) cell protection. This is objective enablement, and no more is required by the law.

In addition, the generalized attacks on gene therapy fall short of the standard set out by the PTO and enforced by the Federal Circuit. It is clear that the PTO is applying an FDA-like analysis of the technology where the only satisfactory showing is one that involves clinical data. This ignores the fact that the law does not require such a showing and, in addition, that gene therapy need not be proved up as usefull over and over again. More specific concerns, such as targeting and delivery, can be addressed by the skilled artisan when considering appropriate vectors and formulations.

The art rejection relies on, rather than gene therapy, the provision of a single polypeptide (TNF-α), in combination with subsequent radation treatment. The distinctions between this art and the present invention, which relies on ***constitutive*** expression ***within*** a cell, are evident. This art, even with supporting documents that show expression of recombinant TNF-α, fall far short of what is needed to

show obviousness. A key element -- likelihood of success -- cannot be extracted from this art given the stated differences and the lack of any indication that substituting gene therapy for protein therapy would be effective. Moreover, even if the examiner had made out a *prima facie* case, the surprising and unexpected results which show synergistic killing from the combination of TNF-α and radiation clearly would provide a sufficient rebuttal.

IX. ARGUMENT

A. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 2-6 are rejected for the recitation of "increasing" the transcription of a constitutive promoter. The claims have either been canceled or amended to delete any mention of increasing, thereby obviating the rejection. Thus, it is believed that the rejection is moot.

Claims 1, 7-30 and 35 are rejected because the claims are alleged to be overly broad. It appears to be the examiner's position that claims not limited to particular polypeptides would require undue experimentation to determine which could be used therapeutically. Appellants respectfully traverse.

The principle underlying the present invention is the provision, in a constitutive fashion, of a polypeptide to cells in conjunction with radiotherapy. In a first embodiment, the polypeptide augments the action of radiotherapy by sensitizing the cell to the effects of radiation. In a second embodiment, the polypeptide protects the cell from harmful radiation effects. Thus, the present invention, indeed, covers these two broad concepts.

The examiner appears to argue that, not only must the claims be narrowed to particular polypeptides that would accomplish these tasks, but that appellants should provide proof that each of these polypeptides works as predicted, both *in vitro* and *in vivo*. On the other hand, the examiner has not indicated that such polypeptides do not exist or that such polypeptides could not achieve radiosensitizing or radioprotective effects. It also should be pointed out that the claims are limited to situations where the polypetides do, in fact, provide the asserted sensitizing or protective effects. Finally, the specification provides sufficient guidance to determine which polypeptides provide the radioprotective and radiosensitizing effects. See, for example, pages 22-23 and Examples I and II. In the absence of such a showing, appellants submit that there is no *prima facie* reason to doubt the disclosure in this regard.

Similarly, has the examiner has not challenged the showing, provided in the specification, that TNF-α acts in conjunction with radiation to effect cell killing. Pages 34-36 of the instant specification illustrate that TNF-α functions according the present invention. For example, sublethal concentrations of TNF-α enhanced killing by radiation in certain cell lines, sometime in an additive fashion (STSAR-33) and sometimes in a synergistic fasion (SQ-20B). Further, the combination of radiation and TNF-α results in the induction of apoptosis in a significant portion of cells so treated, at levels and concentrations, respectively, that would not induce apoptosis when given alone. Thus, claims reciting TNF-α should be considered separately patentable over this aspect of the rejection given that data has, in fact, been provided to support these claims.

The first paragraph of §112 requires no more than objective enablement, and it is up to the examiner to provide sufficient reason and/or evidence to doubt the enabling quality of the specification. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971); *In re Dinh-Nguyen*, 181 USPQ 46 (CCPA 1974). Here the examiner has done no more than to allege overbreadth and indicate that it would not be possible to extrapolate from *in vitro* testing (which is admitted not to be undue) to *in vivo* results. There is no evidence of record, however, as to why one would not accept the finding, *in vitro*, that a compound is radioprotective or radiosensitizing as predictive of what would happen *in vivo*. Surely, there may be different results going from a tissue culture dish to a whole organism, but would this completely denude the *in vitro* data of predictive value? The answer surely must be no.

Revisiting the first Office Action, the "reasoning" provided therein falls short. Primarily, the examiner argues difficulty with respect only to delivery and targeting of genetic constructs. While it must be admitted that gene therapy is not a trivial endeavor, it similarly must be recognized that the difficulties described by the references have not deterred the field. There are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. In reviewing this topic, it is not accurate to focus only on the technical hurdles faced by the field, and to ignore the successes. Previously submitted were articles by Blaese *et al.* (1995), Roth *et al.* (1996) and R. Crystal (1995), all of which describe successful gene therapy trials.

It also should be pointed out that the examples track the use of adenovirus as a particular vector for delivery of the therapeutic radioprotective and radiosensitizing genes. Adenovirus is

one of the most popular gene therapy vehicles, and there can be no question that one of skill in the art would believe that gene delivery *in vivo* using this construct would be deemed operative, even in the absence of clinical data. Again, adenovirus as a delivery vehicle is separately patentable over the examiner's reasoning.

It also should be noted that the specification, in fact, contains a significant amount of information about how to deliver and target genetic constructs to a patient. For example, see page 17, lines 25-29 (doses and route of delivery for adenovirus), page 18, lines 9-21 (formulations), pages 19-20 (liposomes), pages 20-21 (herpesvirus and retrovirus), pages 23-25 (formulations), pages 42-45 (protocol for Phase I clinical trial), pages 49-50 (human gene transfer protocol) and pages 51-52 (clinical protocol for TIL therapy). This disclosure, along with the knowledge and skill of the typical clinician, which is high, certainly permits the use of the present invention *in vivo*.

Moreover, the "enablement" requirement under §112, first paragraph, does not require that a therapy be approved by the FDA, much less provide a complete "cure." Rather, the specification need only show how to make and use the present invention. "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *In re Krimmel*, 130 USPQ 215, 219 (CCPA 1961).

In sum, the examiner has not provided sufficient reason to doubt the enablement of the claimed invention merely based on the "scope" of the claims. Therefore, it is respectfully requested that the Board reverse the rejection.

B. Rejections Under 35 U.S.C. §112, Second Paragraph

Various claims are rejected under the second paragraph of §112 as indefinite. **Claim 1** is said to be indefinite for the recitation of "said cell" without antecedent basis and for the lack of a step where the gene is expressed. Both of these issues have been addressed by amendment. **Claims 4, 5, 7, 15 and 16** are rejected for various reasons but, in order to advance the prosecution, all of these claims have been canceled, thereby obviating the rejections.

C. Rejections Under 35 U.S.C. §103

The examiner has rejected all claims under §103 over Hallahan I or Hallahan II, along with a variety of supporting references. The primary Hallahan references are said to teach provision of TNF-α to cells, mice or humans, followed by the administration of ionizing radiation. The references further are said to teach that this combined therapeutic approach results in enhanced effect of the radiation treatment. The references are acknowledged to be lacking in gene transfer methodology, for which the secondary references are cited (along with various other aspects of dependent claims). In sum, the examiner deems it obvious to transfer a TNF-α gene, as an exemplary radiosensitizing/radioprotective agent, into a cell or a cell of a patient for the purpose of an improved combined therapy approach for the treatment of cancer. Appellants respectfully traverse.

What the examiner is proposing, from both a legal and scientific standpoint, is that the provision of a polypeptide to a cell, animal or patient is reasonably equivalent to the synthesis of that same polypeptide within a cell or with a cell of an animal or a patient. Appellants submit, respectfully, that it would not.

Appellants again point to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), for the appropriate standard in determining obviousness. That case held that, in order for a reference or references to obviate an invention, it must be shown that the references contain (1) detailed enabling methodology for practicing the claimed invention; (2) a suggestion for modifying the prior art to practice the claimed invention; and (3) ***evidence suggesting that the invention would be successful***. It is submitted that this could not be the case here.

In the more recent case of *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck*, the Federal Circuit stated that, in order for an examiner to make out a *prima facie* case of obviousness, at least two things must be shown. First, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition. And second, the prior art must have demonstrated a reasonable expectation of success in practicing the invention. Again, it is submitted that, in light of the discussion above, such is not the case here.

Finally, it is worth noting the *O'Farrell* court's caution regarding the improper "obvious to try" standard. In the decision, it was stated that it is not appropriate for the PTO to inquire,

pursuant to §103, as to "what was 'obvious to try' [in] ... explor[ing] a ... general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell* at 1681. Similarly, where the art provides merely "general guidance as to ... how to achieve" a particular goal, obviousness cannot be found.

Here, at best, the cited references merely present an "obvious to try" situation. Could one have predicted, *a priori*, the effects of combining constitutive TNF gene therapy with radiotherapy? Clearly, the answer is no. That is not to say that one could not have hypothesized a particular outcome, but such is not the definition of obviousness. Absolute predictability is not required, but here, there is nothing to indicate what the likely outcome would be. On this ground alone, appellants respectfully submit that the claimed invention could not be *prima facie* obvious. Furthermore, the examiner has not cited any art that addresses the likelihood of success in practicing the present invention employing the ***constitutive*** provision of a polypeptide from ***within*** the cell. Because of this deficiency, one of skill in the art would not, *a priori*, expect that the results of Hallahan I and II would hold for transgene expression.

The examiner has attempted to rebut this line of argument by pointing to Teng, which shows the expression of TNF in tumor cells *in vitro* and *in vivo*. The results of this paper show that tumor cells transfected with TNF grow at the same rate as untransfected cells *in vitro*, while *in vivo*, the transfected, TNF-secreting cells form smaller tumors than untransfected or transfected, non-secreting cells. This showing only indicates that TNF ***can*** be produced in transfected cells. It does ***not*** show

that TNF will have an effect, in conjunction with radiation, on tumor cells. It is important to note that transfected, non-secreting tumor cells were not inhibited *in vivo*, indicating that the secretory pathway was important in the effect observed. This adds a further level of complexity and unpredictability to the claimed invention.

Moreover, the instant specification shows that the combination of TNF and radiation not only slowed tumor cell growth at a level or above TNF and radiation, alone or in combination, but tumors so treated regressed, presumably from tumor cell killing. See specification at pages 34, 35, for example:

> To determine the possible interactions between TNF-α and x-rays in non-TNF-α producing cels, human epithelial tumor cells (SQ-20B and HNSCC-68) were irradiated 20 hr after TNF-α was added. These cell lines do not produce TNF-α in response to ionizing radiation. TNF-α (1000 units/ml) was cytotoxic to SQ-20B and SCC-61 cells, reducing the PE by 60-80%. The D_0 for cell line SQ-20B with radiation alone is 239 cGy. With TNF-α (1000 units/ml) added 24 hours before x-rays, the D_0 was 130.4 cGy. Therefore, a synergistic interaction (Dewey, 1979) between TNF-α and x-rays was demonstrated in this cell line. TNF-α added after irradiation did not enhance cell killing by radiation in cell lines SQ-20B. Nonlethal concentrations of TNF-α (10 units/ml) resulted in enhanced radation killing in cell line HNSCC-68, providing evidence that TNF-α may sensitize some epithelial as well as mesenchymal tumor cell lines to radiation.

See also pages 45-49 ("TNF greater than 1000 pg/mg protein was produced in tumors treated with virus alone, while 300 pg/mg was detected in irradiated tumors. Tumors treated with both HSV-1 (Egr-TNF) and radiation regressed and did not regrow. The reduction in TNF following radiation was presumed to be due to synergistic killing of infected cells." Page 48, lines 12-17.). This synergistic effect could not have been predicted from Hallahan I or II, Teng, or any of the other references, alone or in combination. Clearly, this constitutes a surprising and unexpected result that militates in favor of

patentability. For this additional reason, appellants submit that claims directed to this aspect of the invention are separately patentable over the art of record.

Thus, given the foregoing comments, appellants respectfully request reversal of the rejections by the Board.

X. SUMMARY AND CONCLUSION

In light of the foregoing remarks, it is respectfully submitted that the appealed claims are enabled, definite and nonobvious. Therefore, reversal of the rejections under 35 U.S.C. §112, first paragraph, 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103 is respectfully requested.

Respectfully submitted,

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APPENDIX 1: PENDING CLAIMS

1. (Twice amended) A process of treating a human cancer patient comprising providing to [said] a cancer cell in said patient a gene encoding a radiosensitizing polypeptide operatively linked to a constitutive promoter and contacting said cell with ionizing radiation, whereby the gene is expressed and the cancer is treated.

2. (Amended) The process of claim 1, wherein the [cell is radiosensitized by increasing the transcription of the] gene is a TNF-α gene.

3. (Amended) The process of claim [1] 18, wherein the [cell is radioprotected by increasing the transcription of] radioprotecting factor is MnSOD, IL-1[,] or IL-2[, or TNF].

4. (Canceled) The process of claim 1, wherein increasing the transcription of a gene that encodes a cell radiosensitizing factor is accomplished by transfecting the cell with a genetic construct comprising a gene that encodes the cell radiosensitizing factor operatively linked to constitutive promoter.

5. (Canceled) The process of claim 4, wherein the cell is radiosensitized by increasing the transcription of the TNF-α gene.

6. (Twice amended) The process of claim [3] 1, wherein the constitutive promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter, or the Egr enhancer/promoter.

7. (Canceled) The process of claim 1, comprising transfecting the cell with said gene encoding said cell radiosensitizing factor and said promoter.

8. (Amended) The process of claim [7] 1, wherein the transfection is by liposomes, adenovirus or HSV-1.

9. The process of claim 8, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

10. The process of claim 8, wherein the transfection is by adenovirus infection.

11. The process of claim 8, wherein the transfection is by HSV-1 infection.

12. A process of sensitizing a cell to the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a gene that encodes a cytokine, wherein said cytokine is synthesized in and secreted from said cell.

13. The process of claim 12, wherein the cytokine gene is positioned under control of a promoter other than an adenovirus promoter.

14. The process of claim 13, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer-promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

15. (Canceled) The process of claim 1, comprising transfecting said cell with said gene encoding said cell radioprotecting factor.

16. (Canceled) The process of claim 15, wherein said gene encodes MnSOD, IL-1, IL-2, or TNF.

17. (Canceled) The process of claim 15, wherein the constitutive promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer-promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin or replication, the β-actin promoter, or the Egr enhancer/promoter.

18. A process of radioprotecting a cell from the effects of ionizing radiation comprising:

(a) obtaining a genetic construct comprising a gene encoding a cell radioprotecting factor operatively linked to a constitutive promoter; and
(b) transfecting the cell with the genetic construct;

whereby said radioprotecting factor is expressed and said cell is protected from said effects.

19. The process of claim 18, wherein the transfecting is by liposomes, adenovirus or HSV-1.

20. The process of claim 19, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

21. The process of claim 19, wherein the transfection is by adenovirus infection.

22. The process of claim 19, wherein the transfection is by HSV-1 infection.

26. A process of radioprotecting a cell from the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a gene encoding a radioprotecting factor in a mammalian cell.

27. The process of claim 26, wherein the gene is positioned under control of a promoter other than an adenovirus promoter.

28. The process of claim 27, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFVs enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

29. (Amended) A pharmaceutical composition comprising a genetic construct comprising a gene that encodes a cell radiosensitizing or radioprotecting factor operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier.

30. (Twice amended) The pharmaceutical composition of claim 29, further defined as comprising the [vector] genetic construct packaged with a virion or virus particle.

31. A method of increasing the level of a radioprotecting or radiosensitizing factor in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 29 or claim 30.

32. The method of claim 31, wherein the administering is by means of an intravenous injection of from 10^8 to 10^{11} virus particles.

33. The method of claim 31, wherein the mammal is a mouse.

34. The method of claim 31, wherein the mammal is a human.

35. (Amended) A process of inhibiting growth of a tumor comprising the steps of:

(a) delivering to said tumor a therapeutically effective amount of a DNA molecule comprising a constitutive promoter operatively linked to a region encoding a polypeptide having the ability to inhibit growth of a tumor cell, which coding region further is operatively linked to a transcription-terminating region, whereby said polypeptide is expressed; and
(b) exposing said cell to an effective dose of ionizing radiation,

whereby the growth of said tumor is inhibited by said polypeptide and ionizing radiation.

36. A method of assessing the response of a cell to the constitutive production of radiosensitizing or radioprotecting factors following ionizing radiation, comprising:

(a) growing the cell in culture;
(b) transfecting the cell with a genetic construct comprising a gene that encodes the cell radiosensitizing factor or radioprotecting factor operatively linked to a constitutive promoter, whereby said polypeptide is expressed;
(c) exposing the cell to an effective dose of ionizing radiation; and
(d) assessing the response of said cell.

APPENDIX 2: EXHIBITS